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Estimation of Toxicity to Marine Species with Structure-Activity Models Developed to Estimate Toxicity to Freshwater Fish

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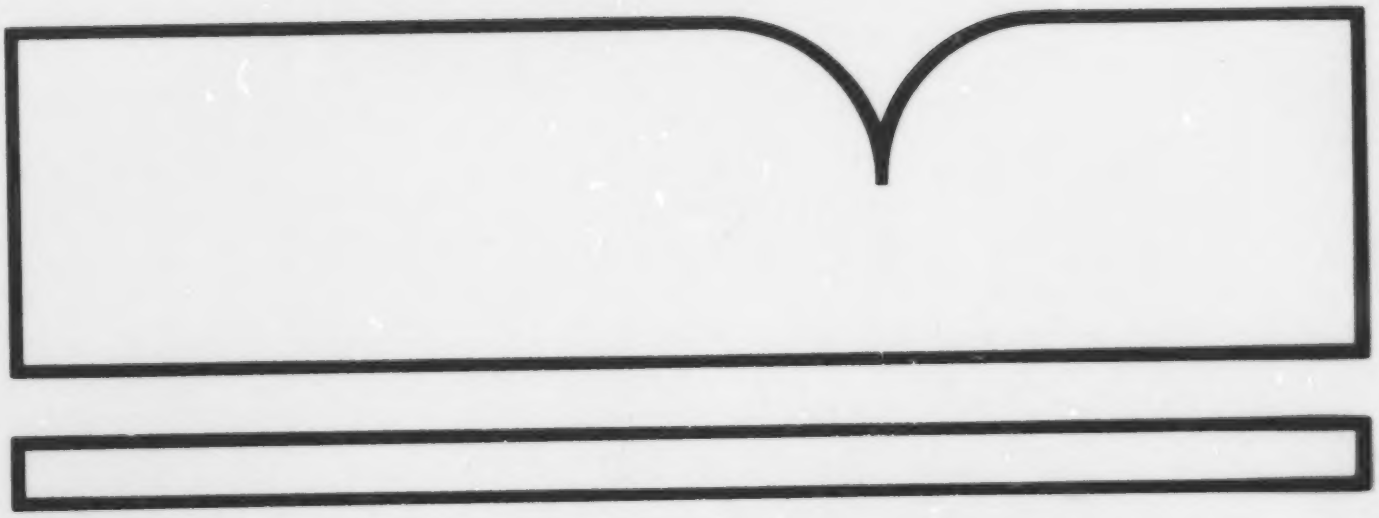

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16. ABSTRACT: Structure-activity models which were developed to estimate toxicity of chemicals to freshwater fish were tested for use with an estuarine fish(Cyprinodon variegatus)and mysids(Mysidopsis bahia). Significant linear and polunomial relationships that correlated well existed between reported 96h LC_{50}values for each marine species and log P (log octanol/water partition coefficient). Good linear relationships were obtained when the toxicity values for C. variegatus and M. bahia were regressed on water solubility. These models were compared to models developed for freshwater fish using log P and log S. Models using log P to estimate acute toxicity for two freshwater fish produced toxicity values similar to those measured for C. Variegatus and M. bahia,wehereas those models developed with water solubility produced values similar to those for C. variegatus, but not for M. bahia. The data indicated that toxicity to C variegatus can be estimated to within an order of magnitude for 58%of the chemicals using freshwater fish models developed with logP and for 77% of the chemicals with those developed with log S. The calculated toxicity values were compared to the measured values for each marine species and those measured for Pimephales promelas and Poecilla reticulata. Calculated toxicity values were generally overestimates of toxicity to marine species.

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ESTIMATION OF TOXICITY TO MARINE SPECIES WITH STRUCTURE-ACTIVITY MODELS DEVELOPED TO ESTIMATE TOXICITY TO FRESHWATER FISH*

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Structure-activity models which were developed to estimate toxicity of chemicals to freshwater fish were tested for use with an estuarine fish (*Cyprinodon variegatus*) and mysids (*Mysidopsis bahia*). Significant linear and polynomial relationships that correlated well existed between reported 96-h LC_{50} values for each marine species and log *P* (log octanol/water partition coefficient). Good linear relationships were obtained when the 96-h LC_{50} values for *C. variegatus* and *M. bahia* were regressed on water solubility (μmol/l). These models were compared to models developed for freshwater fish using log *P* and log *S*. Models using log *P* to estimate acute toxicity for two freshwater fish produced 96-h LC_{50} values similar to those measured for *C. variegatus* and *M. bahia*, whereas, those models developed with water solubility produced 96-h LC_{50} values similar to those for *C. variegatus*, but not for *M. bahia*. The data indicated that models developed with log *P* for freshwater fish can be used to estimate toxicity to *C. variegatus* for a minimum of 58% of the chemicals, whereas models using water solubility estimated toxicity to *C. variegatus* for a minimum of 77% of the chemicals within an order of magnitude for screening purposes. The calculated 96-h LC_{50} values were compared to the measured values for each marine species and those measured for *Pimephales promelas* (fathead minnow) and *Poecilia reticulata* (guppy). Tests indicated generally that calculated 96-h LC_{50} values were overestimates of the measured 96-h LC_{50} values when models for freshwater fish were used to estimate toxicity to each marine species. More data are required for marine species to determine if highly significant relationships between marine and freshwater fish exist with comparisons using larger sample sizes.

Key words: structure-activity models; toxicity; freshwater fish

INTRODUCTION

In considering the problem of evaluating the behavior of industrial chemicals in the aquatic environment, a rapid means of estimating toxicity to marine species through the use of predictive short-term measurements is required. One method

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utilizes structure-activity relationships to compute the toxicity of chemicals with use of the octanol/water partition coefficient (P) (Könemann, 1981). He found that the structure-activity correlation between toxicity (LC_{50}) to guppies *Poecilia reticulata* and (P) of individual chemicals is summarized by the equation:

$$\log 1/LC_{50} = 0.871 \log P - 4.87$$

Veith (1981) reported that chemical activity needed to cause narcosis in the fish *Pimephales promelas* is similar to that needed to cause narcosis in mammals. His data indicated that the fish 96-h LC_{50} for more than 50 organic chemicals could be estimated by the equation:

$$\log 1/LC_{50} = 1.17 + 0.94 \log P$$

Veith et al. (1983) reported that the relationship between 96-h LC_{50} data for *Pimephales promelas* and log P was not best fit by a linear model but was best represented by a polynomial regression equation:

$$\log LC_{50} = -1.10 \log P + 0.05 (\log P)^2 - 1.22$$

This equation was intended as an estimation of toxicity (LC_{50}) for select chemicals having a nonspecific mode of action. The accuracy of predictions made with these models is limited by the inherent variances in toxicity testing and the variations in toxicity of the chemicals to the species tested. In addition, differences in the LC_{50} values among the species tested may be small in comparison to errors intrinsic with structure-activity relationships (SAR). Recognizing these limitations, Veith et al. (1983) indicated that their model is limited to chemicals with a log P less than 4.0. Könemann (1981) indicated that the validity of his model in predicting LC_{50} values for chemicals ended at log $P \approx 6.0$.

The log P of compounds with log $P \geq 4$ are difficult to measure by standard techniques (Veith et al., 1979b). Therefore, HPLC has been used to estimate log P; however, there are problems with this technique since 1 and 2 order-of-magnitude differences between expected and observed log P values are common (Veith et al., 1979a, 1980). Könemann (1981) preferred to use only calculated log P values because of the problems in measurements if log $P \geq 4$. Errors in calculated log P are of the same magnitude as those obtained with HPLC (Hansch and Leo, 1979). There are also problems associated with use of log S. Measurement of water solubility of a compound is also very difficult (Banerjee et al., 1980). Toxicity of compounds that are infinitely soluble in water cannot be estimated with models using water solubility as the SAR. In addition, since ionization decreases the toxicity, it has been suggested that a correction for ionization be considered when estimating toxicity (Saarikoski and Viluksela, 1982). Hansch and Leo (1979) recognized this problem and also recommended that log P be corrected for ionization when used to estimate toxicity. Thus, the range in variability for water solubility data appears to be similar to that for log P.

The variability associated with the relationship between SAR parameters (water solubility and log P) and toxicity to aquatic organisms is also affected by LC_{50} values that exceed the water solubility limit of a compound. Herzel and Murty (1984) reported that carrier solvent does not increase the water solubility of poorly soluble compounds. Herzel et al. (1976) have also shown that in aquatic toxicity tests performed with chemical concentrations equal to or near saturation in water, the evaporation loss was very high. Thus it is evident that in tests where the toxicity exceeds the solubility limit of a chemical, the organism is exposed to chemical concentrations less than those calculated to be present in the test system. Toxicity may also be influenced by biochemical differences in metabolism which are not considered in relationships with log P or log S.

Studies concerned with structure-activity relationships as estimators of toxicity to marine species have not been reported. Therefore, this study was initiated to determine whether models established for the estimation of the 96-h LC_{50} values for freshwater fish using octanol/water partition coefficients or water solubility as the SAR parameter can be used to estimate the 96-h LC_{50} values for marine species.

MATERIALS AND METHODS

The models used to predict toxicity of organic chemicals to freshwater fish and tested in this study for use in predicting toxicity (96-h LC_{50}) for a marine fish (*Cyprinodon variegatus*, sheepshead minnow) and a mysid shrimp (*Mysidopsis bahia*) are shown below as models 1 (Könemann, 1981), 2 (Könemann, 1981) and 3 (Veith et al., 1983):

(1) $\log 1/LC_{50} = -0.698 \log S + 0.09$

Model developed with freshwater guppy (*Poecilia reticulata*)

S = water solubility in μmol/l

(2) $\log 1/LC_{50} = 0.871 \log P - 4.87$

Model developed with freshwater guppy (*Poecilia reticulata*)

(3) $\log LC_{50} = -1.10 \log P + 0.05 (\log P)^2 - 1.22$

Model developed with fathead minnow (*Pimephales promelas*)

Table I contains the reported values for 96-h LC_{50} (μmol/l) and their sources for the chemicals and species used in this study.

Table II contains the reported values for log P and water solubility (μmol/l) in addition to their sources for the chemicals used in this study.

The data outlined in Tables I and II were used for comparisons and model development. These same data were used to test the applicability of models developed for freshwater fish for use in estimating the toxicity (96-h LC_{50}) for *C. variegatus* and *M. bahia*. Linear regression models were fit to data on each marine species and 95% confidence intervals about the slopes were computed. If in fact the slopes of the models reported for freshwater fish fell within the 95% confidence intervals calculated for models developed for the marine species, then the slopes of

TABLE I

96-h LC_{50} values for the respective chemicals and marine species. Units changed from ppm to μmol/l where appropiate and the $\log_{10}$ calculated.

Chemical	Log 96-h LC_{50} (μmol/l)	Species	Reference
1,1,1,2,2,2-Hexachloroethane	1.00	*C. variegatus*	Heitmuller et al., 1981
1,1,1,2,2-Pentachloroethane	2.75		Heitmuller et al., 1981
1,1,1-Trichloroethane	2.72		Heitmuller et al., 1981
1,1-Dichloroethylene	3.41		Heitmuller et al., 1981
1,1,2,2-Tetrachloroethane	1.85		Heitmuller et al., 1981
1,2,3,5-Tetrachlorobenzene	1.23		Heitmuller et al., 1981
1,2,4,5-Tetrachlorobenzene	0.56		Heitmuller et al., 1981
1,2,4-Trichlorobenzene	2.06		Heitmuller et al., 1981
1,2-Dichlorobenzene	1.81		Heitmuller et al., 1981
1,3-Dichlorobenzene	1.72		Heitmuller et al., 1981
1,3-Dichloropropene	1.20		Heitmuller et al., 1981
1,4-Dichlorobenzene	1.69		Heitmuller et al., 1981
2,3-Dinitrotoluene	1.10		Heitmuller et al., 1981
2,4,5-Trichlorophenol	0.93		Heitmuller et al., 1981
2,4,6-Trinitrophenol	2.75		Heitmuller et al., 1981
2,4-Dinitrophenol	2.19		Heitmuller et al., 1981
4-Chlorophenol	1.62		Heitmuller et al., 1981
4-Nitrophenol	2.28		Heitmuller et al., 1981
Benthiocarb	0.68		Schimmel et al., 1983
Bromoform	1.85		Heitmuller et al., 1981
Chlorobenzene	1.94		Heitmuller et al., 1981
Chloropyrifos	0.40		Schimmel et al., 1983
Diazinon	0.68		Goodman et al., 1979
Dibenzofuran	1.02		Heitmuller et al., 1981
Dieldrin	−1.58		Parrish et al., 1973
Diethyl phthalate	2.13		Heitmuller et al., 1981
Dimethyl phthalate	2.47		Heitmuller et al., 1981
Diphenyl ether	1.14		Heitmuller et al., 1981
Disulfoton	0.43		Kenaga, 1979
Ethion	−0.74		Kenaga, 1979
Fenvalerate	−2.00		Schimmel et al., 1983
Heptachlor	−2.00		Schimmel et al., 1976
Hexachlorobutadiene	0.32		U.S. EPA 440/5-80-053, 1980
Kepone	0.15		Schimmel and Wilson, 1977
Lindane	0.44		Schimmel et al., 1977
Methoxychlor	−0.85		Parrish et al., 1977
Methylene chloride	3.58		Heitmuller et al., 1981
Nitrobenzene	2.68		Heitmuller et al., 1981
Pentachlorobenzene	0.		Heitmuller et al., 1981
Permethrin	−0.76		Schimmel et al., 1983

TABLE I (*Continued*)

96-h LC_{50} values for the respective chemicals and marine species. Units changed from ppm to μmol/l where appropiate and the $\log_{10}$ calculated.

Chemical	Log 96-h LC_{50} (μmol/l)	Species	Reference
1,2,3,5-Tetrachlorobenzene	0.19	*M. bahia*	U.S. EPA 440/5-80-028, 1980
1,2,4,5-Tetrachlorobenzene	0.83		U.S. EPA 440/5-80-028, 1980
1,2,4-Trichlorobenzene	0.39		U.S. EPA 440/5-80-028, 1980
1,3-Dichloropropane	1.95		U.S. EPA 440/5-80-043, 1980
AC 222,705	-3.69		Schimmel et al., 1983
Acenaphthene	-0.79		U.S. EPA 440/5-80-015, 1980
Benthiocarb	0.10		Schimmel et al., 1983
Chlorobenzene	2.16		U.S. EPA 440/5-8-028, 1980
Dieldrin	-1.88		U.S. EPA 440/5-80-019, 1980
Endosulfan	-2.52		S. Gentile, pers. comm.
EPN	-2.00		Schimmel et al., 1979
Fenvalerate	-3.69		Schimmel et al., 1983
Heptachlor	-2.09		U.S. EPA 440/5-80-052, 1980
Hexachlorobutadiene	-0.63		U.S. EPA 440/5-80-053, 1980
Leptophos	-2.09		Schimmel et al., 1979
Lindane	-1.69		Schimmel et al., 1977
Pentachlorobenzene	-0.19		U.S. EPA 440/5-80-028, 1980
Tetrachloroethylene	1.78		U.S. EPA 440/5-80-073, 1980
Toluene	2.78		U.S. EPA 440/5-80-075, 1980

the lines were considered statistically not different. If the slope of a marine model was found to be statistically not different from the slope of the freshwater model developed with the same SAR parameter, it was considered statistically valid to use these models interchangeably.

RESULTS AND DISCUSSION

In Table III are summarized the results obtained when log LC_{50} was regressed on log octanol/water partition coefficient (log *P*) or water solubility (μmol/l). Significant ($\alpha < 0.01$) linear and polynomial relationships existed between the 96-h LC_{50} for *C. variegatus* and *M. bahia* and log *P* for the chemicals listed in Tables I and II. In addition, significant ($\alpha < 0.01$) linear relationships were obtained between the 96-h LC_{50} for *C. variegatus* and *M. bahia* and water solubility for the chemicals in Tables I and II. The correlation coefficients (r) for the linear models derived with water solubility were higher for *C. variegatus* ($r = 0.91$) and *M. bahia* ($r = 0.88$), than those for the linear models derived with log *P* for *C. variegatus* ($r = 0.81$) and *M. bahia* ($r = 0.84$). No improvement occurred with the introduction of $(\log P)^2$

TABLE II

Log *P* and log *S* values for the respective chemicals used in this study.

Chemical	Log *P*	Reference	Log *S*[a]	Reference
1,1,1,2,2,2-Hexachloroethane	1.91	Veith et al., 1980		
1,1,1,2,2-Pentachloroethane	2.89	Veith et al., 1980		
1,1,1-Trichloroethane	2.47	Veith et al., 1980	3.57	Callahan et al., 1979
1,1-Dichloroethylene	1.48	Callahan et al., 1979	3.61	Callahan et al., 1979
1,1,2,2-Tetrachloroethane	2.39	Veith et al., 1980	0.24	Banerjee et al., 1980
1,2,3,5-Tetrachlorobenzene	4.46	Veith et al., 1980	0.26	Banerjee et al., 1980
1,2,4,5-Tetrachlorobenzene	4.67	Kenaga and Goring, 1980	1.44	Kenaga and Goring, 1980
1,2,4-Trichlorobenzene	4.23	Veith et al., 1979a	2.21	Callahan et al., 1979
1,2-Dichlorobenzene	3.40	Veith et al., 1980	2.99	Callahan et al., 1979
1,3-Dichlorobenzene	3.44	Veith et al., 1980	2.92	Callahan et al., 1979
1,3-Dichloropropane	2.28	Hansch et al., 1968	1.38	Hansch et al., 1968
1,3-Dichloropropene	1.98	Callahan et al., 1979		
1,4-Dichlorobenzene	3.38	Veith et al., 1979a	2.37	Chiou et al., 1977
2,3-Dinitrotoluene	1.98	Callahan et al., 1979		
2,4,5-Trichlorophenol	3.72	Veith et al., 1979a		
2,4,6-Trinitrophenol	2.03	Leo et al., 1971		
2,4-Dinitrophenol	1.53	Callahan et al., 1979	4.48	Callahan et al., 1979
4-Chlorophenol	2.35	Veith and Morris, 1979		
4-Nitrophenol	1.91	Callahan et al., 1979		
Acenaphthene	4.49	Veith et al., 1980	0.67	Banerjee et al., 1980
Benthiocarb	3.40	Schimmel et al., 1983		
Bromoform	2.30	Callahan et al., 1979	4.09	Callahan et al., 1979
Chlorobenzene	3.79	Veith et al., 1979a	3.63	Chiou et al., 1977
Chlorpyrifos	4.82	Veith et al., 1979a	0.05	Chiou et al., 1977
Diazinon	3.14	Kanazawa, 1980	2.12	Kenaga and Goring, 1980
Dibenzofuran	4.12	Veith et al., 1979a	0.77	Banerjee et al., 1980
Dieldrin	4.31	Kanazawa, 1980	−1.22	Kenaga and Goring, 1980
Diethyl phthalate	1.40	Veith et al., 1980	3.60	Callahan et al., 1979

TABLE II (*Continued*)

Log *P* and log *S* values for the respective chemicals used in this study.

Chemical	Log *P*	Reference	Log *S*[a]	Reference
Dimethyl phthalate	1.61	Veith et al., 1980	4.34	Callahan et al., 1979
Diphenyl ether	4.21	Veith et al., 1979a	2.09	Callahan et al., 1979
Disulfoton	3.81	Kenaga and Goring, 1980	1.96	Kenaga and Goring, 1980
Endosulfan			−0.39	Callahan et al., 1979
EPN	3.85	Kanazawa, 1982		
Ethion			0.71	Kenaga and Goring, 1980
Fenvalerate	6.20	Schimmel et al., 1983	−1.22	Schimmel et al., 1983
Heptachlor	5.44	Veith et al., 1979a	−1.09	Schimmel et al., 1983
Hexachlorobutadiene	3.74	Callahan et al., 1979	0.66	Callahan et al., 1979
Kepone	6.08	Veith, 1982	0.78	Kenaga, 1980
Leptophos	6.31	Chiou et al., 1977	−2.00	Chiou et al., 1977
Lindane	3.89	Veith et al., 1979a	−0.28	Kenaga, 1980
Methoxychlor	4.68	Kenaga and Goring, 1980	−2.04	Kenaga and Goring, 1980
Methylene chloride	1.25	Callahan et al., 1979		
Nitrobenzene	1.83	Veith et al., 1980	4.18	Callahan et al., 1979
Pentachlorobenzene	4.94	Veith et al., 1980	0.72	Banerjee et al., 1980
Permethrin	6.50	Schimmel et al., 1983	−0.95	Schimmel et al., 1983
Tetrachloroethylene	2.60	Chiou et al., 1977	3.38	Chiou et al., 1977
Toluene	2.21	Veith et al., 1980	3.76	Callahan et al., 1979

[a]Units changed to μmol/l where appropriate and $\log_{10}$ calculated.

TABLE III

Linear and polynomial models and 95% confidence intervals on the slope of the line obtained when log LC_{50} or its reciprocal were regressed on log P or log S using data from Tables I and II for *C. variegatus* and *M. bahia*.

Model	Correlation coefficient (r)	Level of significance (α)	Sample size (n)	95% Confidence interval
	Cyprinodon variegatus (sheepshead minnow)			
(4) log $1/LC_{50} = 0.32 - 0.71 \log S$[a]	0.91	<0.01	30	-0.71 ± 0.12
(5) log $1/LC_{50} = 0.73 \log P$[b] $- 3.69$	0.81	<0.01	37	0.73 ± 0.18
(6) log $LC_{50} =$ $-0.335 \log P - 0.055 (\log P)^2 + 3.087$	0.82	<0.01	37	-0.335 ± 0.87 -0.055 ± 0.12
	Mysidopsis bahia (mysid shrimp)			
(7) log $1/LC_{50} = 1.05 - 0.999 \log S$	0.88	<0.01	17	-0.999 ± 0.30
(8) log $1/LC_{50} = 1.25 - \log P - 4.83$	0.84	<0.01	17	1.250 ± 0.45
(9) log $LC_{50} =$ $-2.02 \log P + 0.089 (\log P)^2 + 6.33$	0.84	<0.01	17	-2.020 ± 3.16 0.089 ± 0.185

[a] S = water solubility (μmol/l).
[b] P = octanol/water partition coefficient.

term onto the linear model for either species as indicated by the correlation coefficients (r = 0.82 and 0.84 for *C. variegatus* and *M. bahia*, respectively) (Table III). Könemann (1981) also found that introduction of $(\log P)^2$ onto his linear model did not improve the relationship.

Chiou et al. (1977) and Könemann (1981) have reported on the use of log water solubility (log S) in place of log P in development of linear models for estimation of the 96-h LC_{50} for freshwater fish. The successful use of solubility in structure-activity relationships (SAR) is not unexpected since Hansch et al. (1968), Chiou et al. (1977) and Mackay (1977) reported that log P and log S correlate well. We also obtained a good correlation (r = 0.82, $\alpha < 0.01$) when all log P data in Table II were regressed linearly on all water solubility data in Table II. Könemann (1981) suggested that log P was a better parameter for his SAR models, since his solubility data came from different sources, whereas log P data were calculated by the same method. The high correlation coefficients derived with solubility data from different sources justified the potential use of solubility data in a SAR for *C. variegatus* and *M. bahia* in this study. Therefore, SAR models for freshwater fish which were developed with both log S and log P were tested as estimators of toxicity of compounds to marine species.

Statistical tests were performed to determine whether a significant relationship existed between models for freshwater fish (models 1–3) and those models derived in

this study for *C. variegatus* and *M. bahia* (Table III, models 4–9). Equality of the models derived for freshwater fish and those derived for the marine species was tested by determining the 95% confidence intervals for the slopes of the marine models. Although the slope of model 1 did not fall within the 95% confidence interval of the slope of model 7, which was developed with log *S* for *M. bahia*, the slope of model 1 (−0.698) was extremely close to the upper boundary of the 95% confidence interval (−0.699) for model 7 (Table III). Since the slope of model 1 was marginal to the 95% confidence interval, it was considered outside the 95% confidence interval and the slopes of model 1 and 7 were considered statistically different for this study. However, the slope of model 1 does fall within the 95% confidence interval of the model developed with log *S* for *C. variegatus* (model 4, Table III). Thus, the slopes of the lines represented by models 1 and 4 are not statistically different. Since the lines of both freshwater fish models (linear and polynomial), which were derived with log *P*, fell within the 95% confidence intervals for the comparable marine models, the slopes of the lines are not statistically different (Table III). Thus, the linear model 2 for freshwater fish is neither statistically different from the linear model 5 for *C. variegatus* nor from the linear model 8 for *M. bahia*. In addition, the polynomial models for fathead minnows and the two marine species (models 3, 6, and 9) are statistically indistinguishable. However, the relatively large confidence intervals, which are due to the small sample sizes, lessen the likelihood of rejection and increase the probability of falsely concluding that no difference exists between the models. These results suggest that while we cannot reject the use of models for freshwater fish to predict the 96-h LC_{50} of a chemical for *C. variegatus* and *M. bahia*, we must recognize the inherent differences associated with these relationships.

An attempt was made to reduce the variability inherent in data from different sources by analyzing data from a single source. Sufficient *C. variegatus* toxicity data from a single source (Heitmuller et al., 1981) could be extracted from the literature to allow linear regression analyses with log *P* data from each of two different single sources (Veith et al., 1979b, 1980; Könemann, 1981). In addition, enough toxicity data from a single source was available for *C. variegatus* to allow meaningful linear regression analyses with log *S* data from a single source. However, sufficient log *S*, log *P* and toxicity data from a single source for *M. bahia* were not available for regression analyses.

Significant relationships were obtained with all comparisons using data from single sources. However, when log *P* data of Veith et al. (1979b, 1980) were regressed on single source toxicity data for *C. variegatus* (Heitmuller et al., 1981), greater variability occurred with this data ($r = 0.67$, $\alpha < 0.01$, $n = 15$) than with log *P* and toxicity data from different sources ($r = 0.81$, $\alpha < 0.01$, $n = 37$). This result was contrary to expectations. Less variability and a better correlation ($r = 0.89$, $\alpha < 0.01$, $n = 9$) occurred with a linear regression using Könemann's (1981) log *P* data and toxicity data for *C. variegatus* from Heitmuller et al. (1981)

than when all data from different sources were used ($r = 0.81$, $\alpha < 0.01$, $n = 9$). This was expected; however, the better correlation could be due to the much smaller sample size. That Könemann's (1981) log *P* values offered a better correlation with toxicity than did those values reported by Veith et al. (1979b, 1980) may be due to the fact that Könemann's (1981) log *P* values were obtained by a single method, whereas, Veith et al. (1979b, 1980) obtained theirs from several sources. Therefore, greater inherent variability may be associated with log *P* determinations than with fish LC_{50} values. In contrast, when log *S* data (Könemann, 1981) was regressed linearly on *C. variegatus* toxicity data (Heitmuller et al., 1981), no improvement ($r = 0.91$, $\alpha < 0.01$, $n = 9$) in the relationship was obtained relative to data from different sources ($r = 0.91$, $\alpha < 0.01$, $n = 30$). This occurred despite the much smaller sample size with single source data. On the strength of these comparisons, it appears that water solubility is more successful as a SAR parameter than log *P* regardless of data source.

To determine how well the measured toxicity values for *C. variegatus* and *M. bahia* agreed with toxicity values calculated with models 1, 2 or 3, data from Tables IV–VII were plotted in Figs. 1–3. The closer these values fall about a 45° line (log measured toxicity = log calculated toxicity), the better the agreement between LC_{50} predicted for freshwater fish and measured values for *C. variegatus* and *M. bahia*. It is evident in Fig. 1 that when log *P* was used as the SAR parameter, better agreement between calculated and measured LC_{50} values for *C. variegatus* was obtained with the polynomial model 3 than with the linear model 2, both of which were derived with data for freshwater fish. In contrast, neither the polynomial model 3 nor the linear model 2 provided calculated LC_{50} values which correlated well with measured LC_{50} values for *M. bahia* (Fig. 2). The improvement between calculated and measured LC_{50} values for *C. variegatus* and *M. bahia* was apparent when the two models (models 2 and 3) which used log *P* as a SAR parameter were replaced with the linear model 1 which was derived with log *S* (Fig. 3). Also apparent in Figs. 1–3 was the bias downward from the line $\log x = \log y$ with each model and species. This was indicative of the calculated values being overestimates of the measured LC_{50} values.

To demonstrate more clearly the capacity of freshwater models to estimate 96-h LC_{50} values for *C. variegatus* and *M. bahia*, models 1–3 were used to calculate 96-h LC_{50} values for these two marine species. The calculated 96-h LC_{50} values were compared to the measured 96-h LC_{50} for each marine species and to those measured for *P. promelas* and *P. reticulata* (Tables IV and V). These data indicated that log LC_{50} can be estimated for *C. variegatus* with model 2 within an order of magnitude for a minimum of 58% of the compounds having a range of 3,000,000 in the partition coefficient (Table VIII). Some inprovement in the estimate was observed with the polynomial model (61%) when compared to the linear model derived with log *P* (58%) (Table VIII). However, the highest percentage (77%) was obtained with model 1 which was derived with solubility data (Table VIII). The percentage of

TABLE IV

Estimation of 96-h LC_{50} (μmol/l) for *C. variegatus* using log *P* and models derived for freshwater fish *P. promelas* and *P. reticulata*.

Chemical	*C. variegatus*		*P. promelas*	*P. reticulata*
	Log LC_{50} calculated		Log LC_{50} measured (μmol/l)	Log LC_{50}[c] measured (μmol/l)
	Model 2	Model 3		
1,1,1,2,2,2-Hexachloroethane	3.20	2.86		
1,1,1,2,2-Pentachloroethane	2.36	2.02		
1,1,1-Trichloroethane	2.72	2.37		3.00
1,1-Dichloroethylene	3.58	3.26		
1,1,2,2-Tetrachloroethane	2.78	2.43	2.08[a]	
1,2,3,5-Tetrachlorobenzene	0.98	0.87		0.57
1,2,4,5-Tetrachlorobenzene	0.81	0.73		0.15
1,2,4-Trichlorobenzene	1.18	1.02	1.20[a]	1.12
1,2-Dichlorobenzene	1.91	1.61		1.60
1,3-Dichlorobenzene	1.87	1.59	1.72[a]	1.70
1,3-Dichlorobenzene	3.14	2.79	1.56[b]	1.43
1,4-Dichlorobenzene	1.92	1.63	1.43[a]	
2,3-Dinitrotoluene	3.14	2.79		
2,4,5-Trichlorophenol	1.63	1.38		
2,4,6-Trinitrophenol	3.10	2.75		
2,4-Dinitrophenol	3.53	3.21		
4-Chlorophenol	2.82	2.47		
4-Nitrophenol	3.20	2.86		
Benthiocarb	1.91	1.61		
Bromoform	2.86	2.51		
Chlorobenzene	1.57	1.32	2.45[b]	2.23
Chlorpyrifos	0.67	0.64		
Diazinon	2.13	1.82	1.60[b]	
Dibenzofuran	1.28	1.10		
Dieldrin	1.11	0.97	−1.96[b]	
Diethyl phthalate	3.65	3.38		
Dimethyl phthalate	3.46	3.14		
Diphenyl ether	1.20	1.04	1.38[a]	
Disulfoton	1.55	1.31		
Fenvalerate	−0.52	−0.11		
Heptachlor	0.13	0.27	−0.82[b]	
Hexachlorobutadiene	1.61	1.36	−0.42[b]	
Kepone	−0.41	−0.06	−0.16[b]	0.18
Lindane	1.48	1.25	−0.32[b]	
Methoxychlor	0.79	0.72	−1.59[b]	
Methylene chloride	3.78	3.48		
Nitrobenzene	3.27	2.93		
Pentachlorobenzene	0.57	0.56		−0.15
Permethrin	−0.78	−0.25	−1.36[b]	

[a]Veith et al., 1983.
[b]U.S. EPA, 1980.
[c]Könemann, 1981.

TABLE V

Estimation of 96-h LC_{50} (μmol/l) *C. variegatus* using water solubility (μmol/l) and a model derived for a freshwater fish *P. reticulata*.

Chemical	*C. variegatus*	*P. reticulata*[a]
	Log LC_{50} calculated (Model 1)	Log LC_{50} measured (μmol/l)
1,1,1-Trichloroethane	2.21	3.00
1,1-Dichloroethylene	2.24	
1,1,2,2-Tetrachloroethane	0.08	
1,2,3,5-Tetrachlorobenzene	-0.12	0.57
1,2,4,5-Tetrachlorobenzene	0.70	0.15
1,2,4-Trichlorobenzene	1.25	1.12
1,2-Dichlorobenzene	1.80	1.60
1,3-Dichlorobenzene	1.75	1.70
1,4-Dichlorobenzene	1.61	1.43
2,4-Dinitrophenol	2.86	
Bromoform	2.58	
Chlorobenzene	2.25	2.23
Chlorpyrifos	-0.27	
Diazinon	1.18	
Dibenzofuran	0.23	
Dieldrin	1.18	
Diethyl phthalate	2.24	
Dimethyl phthalate	2.76	
Diphenyl ether	1.16	
Disulfoton	1.07	
Ethion	0.18	
Fenvalerate	-1.18	
Heptachlor	-1.09	
Hexachlorobutadiene	0.15	
Kepone	0.23	0.18
Lindane	-0.52	
Methoxychlor	-1.77	
Nitrobenzene	2.65	
Pentachlorobenzene	0.19	-0.15
Permethrin	1.00	

[a] Könemann, 1981.

estimates for *M. bahia* was much less than that for *C. variegatus*, with model 1 giving the greatest percentage (53%) of log LC_{50} values within an order of magnitude of the measured values (Table VIII). Both models 2 and 3 which were derived with log *P* gave much lower percentages for *M. bahia* than the model derived with log *S* (Table VIII).

Könemann (1981) and Veith et al. (1983) indicated that their SAR models are most effective in predicting the toxicity to fish if the chemicals have a nonspecific

TABLE VI

Estimation of the 96-h LC_{50} (μmol/l) for *M. bahia* using log *P* and models derived for freshwater fish *P. promelas* and *P. reticulata*.

Chemical	*M. bahia*		*P. promelas*	*P. reticulata*
	Log LC_{50} calculated		Log LC_{50} measured (μmol/l)	Log LC_{50}[c] measured (μmol/l)
	Model 2	Model 3		
1,2,3,5-Tetrachlorobenzene	0.98	0.86		0.57
1,2,4-Trichlorobenzene	1.18	1.02	1.20[a]	1.12
1,3-Dichlorobenzene	2.88	2.53	3.06[b]	2.87
AC 222,705	−0.52	−0.11		
Acenaphthene	0.96	0.85		
Benthiocarb	1.91	1.62		
Chlorobenzene	2.40	2.07	2.45[b]	2.23
Dieldrin	1.12	0.97	1.96[b]	
EPN	1.52	1.29		
Fenvalerate	−0.52	−0.11		
Heptachlor	0.13	0.28	−0.82[b]	
Hexachlorobutadiene	1.61	1.37	−0.42[b]	0.18
Leptophos	−0.61	−0.17		
Lindane	1.48	1.26	−0.32[b]	
Pentachlorobenzene	0.35	0.42		−0.15
Tetrachloroethylene	2.60	2.26	1.90[a]	
Toluene	2.94	2.59	0.61[b]	2.87

[a] Veith et al., 1983.
[b] U.S. EPA, 1980.
[c] Könemann, 1981.

or narcotizing effect. The compounds used in this study included those which have specific and nonspecific (narcotic) effects. Therefore, the effects of pesticide data exclusion from calculations were examined (Table IX). With the exception of model 1 with *C. variegatus*, an improvement was obtained. The greatest improvement occurred with *M. bahia* and model 3 whereas the least improvement was obtained with *C. variegatus* using model 2 (Table IX). No improvement occurred with *C. variegatus* and model 1, in fact, a decrease in quality was noted (Table IX). Thus, regardless of chemical category, model 1 which was derived with water solubility data for *P. reticulata* consistently produced a high percentage of 96-h LC_{50} estimates for *C. variegatus* which are within an order of magnitude of the measured values. In addition, model 1 with pesticides which gave a percentage estimate included was as good as that obtained with models 2 and 3 with pesticide data excluded (Tables VIII and IX). After deletion of the pesticide data, the number of compounds for comparisons decreased by approximately 50% (Table IX). Since the number of chemicals used to estimate the 96-h LC_{50} for *M. bahia* in Table IX was small (8–9), the significance of these results is questionable.

TABLE VII

Estimation of the 96-h LC_{50} (μmol/l) for *M. bahia* using water solubility (μmol/l) and a model derived for a freshwater fish *P. reticulata*.

Chemical	*M. bahia*	*P. reticulata*[a]
	Log LC_{50} calculated Model 1	Log LC_{50} measured (μmol/l)
1,2,3,5-Tetrachlorobenzene	−0.12	0.57
1,2,4,5-Tetrachlorobenzene	0.70	0.15
1,2,4-Trichlorobenzene	1.25	1.12
1,3-Dichloropropene	0.66	2.87
AC 222,705	−0.94	
Acenaphthene	0.16	
Chlorobenzene	2.23	2.23
Dieldrin	−1.18	
Endosulfan	−0.60	
Fenvalerate	−1.18	
Heptachlor	−1.09	
Hexachlorobutadiene	0.30	0.18
Leptophos	−1.74	
Lindane	−0.52	
Pentachlorobenzene	−0.51	−0.15
Tetrachloroethylene	2.08	
Toluene	2.35	2.87

[a] Könemann, 1981.

TABLE VIII

Percentage of 96-h LC_{50} values for *C. variegatus* and *M. bahia* that were estimated within an order of magnitude of the measured values by models for freshwater fish.

Species	Model	%	*n*
C. variegatus	1	77	30
C. variegatus	2	58	39
C. variegatus	3	61	39
M. bahia	1	53	17
M. bahia	2	41	17
M. bahia	3	35	17

Toxicity models developed with freshwater fish (eqns. 1–3) did not estimate chemical toxicity to *M. bahia* nearly as well as these same models did for *C. variegatus* (Tables VIII and IX). This was unexpected since *M. bahia* measured toxicities correlated well ($r = 0.94$, $n = 16$) with *C. variegatus* measured toxicities. In addition these same toxicity data for *M. bahia* correlated well with *P. reticulata* (*r*

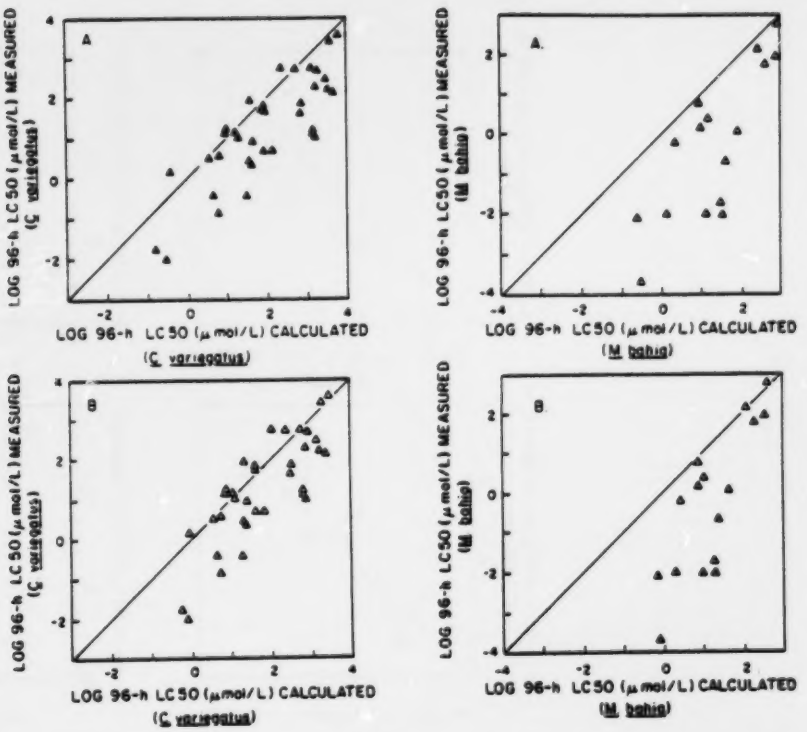

Fig. 1. Plots of measured 96-h LC_{50} values against 96-h LC_{50} values calculated with models 2 and 3, showing the fit about the line $\log y = \log x$ for *C. variegatus*.

Fig. 2. Plots of measured 96-h LC_{50} values against 96-h LC_{50} values calculated with models 2 and 3, showing the fit about the line $\log y = \log x$ for *M. bahia*.

TABLE IX

Percentage of 96-h LC_{50} values for *C. variegatus* and *M. bahia* that were estimated within an order of magnitude of the measured values by models for freshwater fish with pesticides excluded.

Species	Model	%	*n*
C. variegatus	1	75	16
C. variegatus	2	70	23
C. variegatus	3	78	23
M. bahia	1	78	9
M. bahia	2	62	8
M. bahia	3	62	8

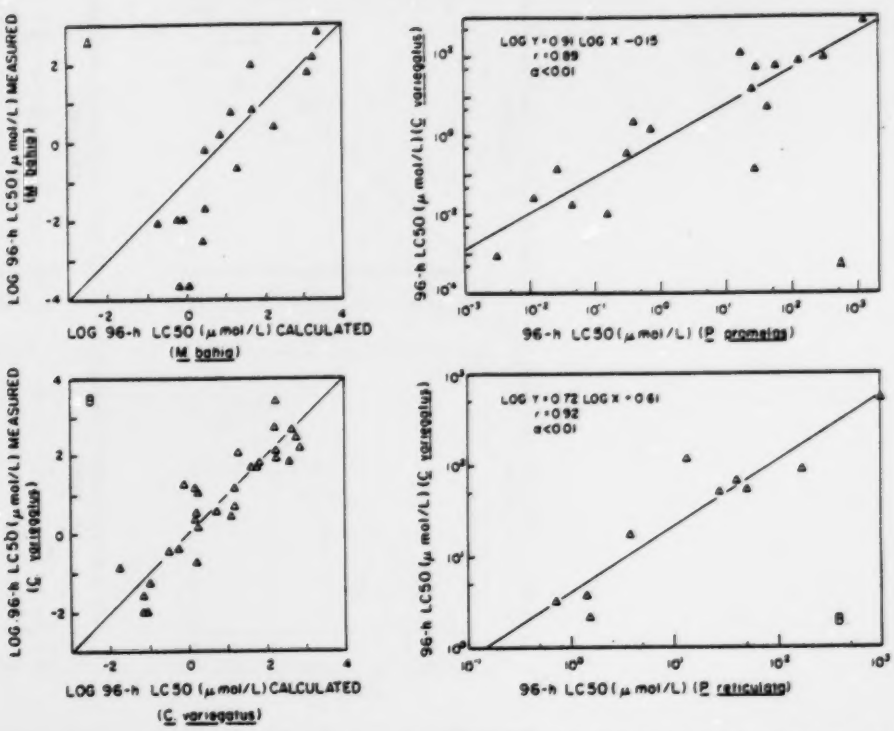
A
LOG 96-h LC50 (μ mol/L) MEASURED (M bahia)
LOG 96-h LC50 (μ mol/L) CALCULATED (M bahia)
LOG Y = 0 91 LOG X − 0 15
r = 0 89
α < 0 01
96-h LC50 (μ mol/L) (C variegatus)
96-h LC50 (μ mol/L) (P promelas)
B
LOG 96-h LC50 (μ mol/L) MEASURED (C variegatus)
LOG 96-h LC50 (μ mol/L) CALCULATED (C variegatus)
LOG Y = 0 72 LOG X + 0 61
r = 0 92
α < 0 01
96-h LC50 (μ mol/L) (C variegatus)
96-h LC50 (μ mol/L) (P reticulata)

Fig. 3. Plots of measured 96-h LC_{50} values against 96-h LC_{50} values calculated with model 1, showing the fit about the line $\log y = \log x$ for *C. variegatus* and *M bahia*.

Fig. 4. Models obtained with data from Tables IV–VII when measured 96-h LC_{50} values for *C. variegatus* were regressed linearly on measured 96-h LC_{50} values for *P. promelas* and *P. reticulata*.

= 0.92, $n = 7$) and *P. promelas* ($r = 0.84$, $n = 9$) toxicity data. Since the relationship between *P. promelas* and *P. reticulata* was excellent (Veith et al., 1983), it was not unexpected that models derived for estimating toxicity to *C. variegatus* would estimate toxicity to *M. bahia* equally as well. In addition, since a strong relationship existed between the toxicity data for *C. variegatus* and *M. bahia*, it would appear reasonable to expect that the models derived for freshwater fish would offer parallel precision in estimating toxicity to *M. bahia*. This contention is supported by the good correlation obtained when *M. bahia* toxicity data were regressed on *P. promelas* toxicity data ($r = 0.84$, $\alpha < 0.01$, $n = 9$). However, the small sample size might allow us to falsely conclude that the freshwater models are good estimators of toxicity to *M. bahia*.

Since the basic tenet of this study was to determine if toxicity models developed

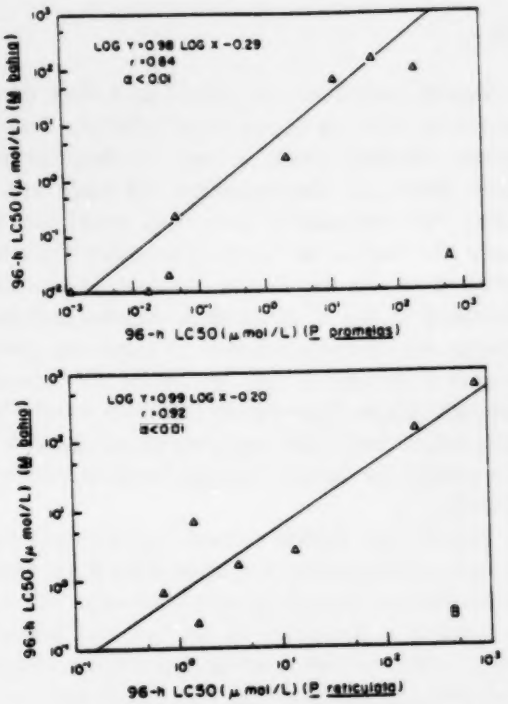
LOG Y = 0.98 LOG X - 0.29
r = 0.84
α < 0.01
96-h LC50 (μ mol/L) (M bahia)
96-h LC50 (μ mol/L) (P promelas)
LOG Y = 0.99 LOG X - 0.20
r = 0.92
α < 0.01
96-h LC50 (μ mol/L) (M bahia)
96-h LC50 (μ mol/L) (P reticulata)
B

Fig. 5. Models obtained with data from Tables IV–VII when measured 96-h LC_{50} values for *M. bahia* were regressed linearly on measured 96-h LC_{50} values for *P. promelas* and *P. reticulata*.

with freshwater fish could be used to estimate toxicity in two marine species, linear regression analyses were performed with data on all chemicals for which 96-h LC_{50} values were available for comparisons among *C. variegatus*, *M. bahia*, *P. promelas* and *P. reticulata* (Figs. 4 and 5). A significant relationship existed between *C. variegatus* and each freshwater fish. The higher correlation was obtained with *P. reticulata* ($r = 0.92$, $\alpha < 0.01$, $n = 10$); however, the relationship between *C. variegatus* and *P. promelas* was also highly significant ($r = 0.89$, $\alpha < 0.01$, $n = 17$) (Fig. 4). Apparent in Fig. 5 was the significant correlation between *M. bahia* and each freshwater fish. An excellent correlation was obtained with *P. reticulata* ($r = 0.92$, $\alpha < 0.01$, $n = 7$), whereas, the relationship with *P. promelas* was not as highly correlated ($r = 0.84$, $\alpha < 0.01$, $n = 9$). Thus, it appears that toxicity data for *C. variegatus* and *M. bahia*, which includes all chemical classes, correlated well with freshwater fish toxicity data that include only compounds which have narcotic effects.

The accuracy of estimations made with the various models in this study is limited by the inherent variances in the toxicity tests, variation due to species differences,

variations associated with use of data from more than one source and variations associated with log *P* and water solubility determinations. However, we feel that greater variability exists in the LC_{50} determinations than in the log *P* determinations, since LC_{50} determinations are made with concentrations of toxicant in the water. No relationships have been established between toxicant concentration in water and that in the tissues. Chemicals which have metabolic routes that are not reflected in the log *P* may produce LC_{50} values inconsistent with the toxicity estimated by log *P*. In addition, factors such as test species, lipid content of test species and temperature can influence the toxicity of a compound. The use of models 1 through 9 may be invalid for compounds that do not penetrate well through tissues or are rapidly lost from water. Therefore, the reasonably good correlations evident in this study are encouraging. It appears that tests other than LC_{50} are needed for better precision in estimation of toxicity to aquatic species with QSARs.

The fact that models derived for freshwater fish can be used to estimate toxicity in select marine species suggested that similar mechanisms may be involved in toxicity of organic chemicals in both freshwater fish and these select marine species. This contention is supported by the fact that highly water soluble chemicals are not highly toxic in either freshwater or marine species, as evidenced by the low toxicity for chemicals with low log *P* values or high water solubility.

Since log *P* and log *S* correlate well with toxicity to selected aquatic species, there is justification for using SAR parameters as estimators of chemical toxicity. However, Kopperman et al. (1974) reported that structure–toxicity relationships are possible only if the chemicals examined have an identical mode of action. In addition, Veith et al. (1983) recognized that prediction models for chemical toxicity to fish were appropriate for chemicals with a narcotic or non-specific mode of toxicity. These same models failed to estimate with the same precision, the toxicity of chemicals with specific modes of toxicity. Könemann (1981) also recognized the fact that chemicals with different modes of action had LC_{50} values that deviated most from the calculated value. These compounds were not included in his calculations. Thus, this selectivity would allow a high correlation coefficient ($r = 0.988$) which he reported for his model. Since the objective of a SAR is to estimate toxicity of an unknown material according to its log *P* or log *S*, outliers should not be removed from a data set unless obvious problems exist with the data. The poorer correlation obtained in this study when compared to that obtained by Veith et al. (1983) and Könemann (1981) is partly attributed to the inclusion of a wider variety of chemicals (including those with specific and nonspecific modes of action).

CONCLUSION

Structure–activity relationships developed previously with acute toxicity data for freshwater fish and partition coefficients or solubilities can be used with some confidence to estimate acute toxicity for marine organisms. Models developed with log

P for freshwater fish estimated the acute toxicity of a minimum of 58% of the chemicals to *C. variegatus* estimate toxicity within an order of magnitude. Models developed for *P. reticulata* using log *S* were superior to those developed with log *P* for estimating toxicity to *C. variegatus* (toxicity was estimated for a minimum of 77% of the chemicals within an order of magnitude), but could not be used for estimation of toxicity to *M. bahia*. Models developed for freshwater fish whether derived with log *P* or log *S* generally overestimated measured toxicity to *C. variegatus* and *M. bahia*. It should be emphasized that these SAR correlations represent only trends and the models developed in this study to estimate toxicity suffer from inaccuracy due to the small number of compounds considered. More data are required for marine species, particularly *M. bahia* to determine if highly significant relationships with freshwater fish exist with comparisons using larger sample sizes.

Predictive models appear to be most suitable as screening tools to focus attention on chemicals that need rigorous testing and are not a substitute for testing.

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